

## PCT COOPERATION TREATY

PCT

## NOTIFICATION OF ELECTION

(PCT Rule 61.2)

From the INTERNATIONAL BUREAU

To:

Assistant Commissioner for Patents  
United States Patent and Trademark  
Office  
Box PCT  
Washington, D.C. 20231  
ETATS-UNIS D'AMERIQUE

in its capacity as elected Office

Date of mailing (day/month/year) 03 August 2000 (03.08.00)	
International application No. PCT/US99/28385	Applicant's or agent's file reference 1719 PCT F
International filing date (day/month/year) 01 December 1999 (01.12.99)	Priority date (day/month/year) 03 December 1998 (03.12.98)
Applicant PANG, Iok-Hou	

1. The designated Office is hereby notified of its election made:

☒ in the demand filed with the International Preliminary Examining Authority on:  
05 June 2000 (05.06.00)

☐ in a notice effecting later election filed with the International Bureau on:

2. The election ☒ was  
☐ was not

made before the expiration of 19 months from the priority date or, where Rule 32 applies, within the time limit under Rule 32.2(b).

The International Bureau of WIPO 34, chemin des Colombettes 1211 Geneva 20, Switzerland Facsimile No.: (41-22) 740.14.35	Authorized officer Antonia Muller Telephone No.: (41-22) 338.83.38
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# PATENT COOPERATION TREATY

RECEIVED

From the INTERNATIONAL SEARCHING AUTHORITY

PCT

MAY 23 2000

To:

ALCON LABORATORIES, INC.  
Attn. MAYO, M.  
6201 South Freeway  
Fort Worth, Texas 76134-2099  
UNITED STATES OF AMERICA

PATENT/ LEGAL  
NOTIFICATION OF TRANSMITTAL OF  
THE INTERNATIONAL SEARCH REPORT  
OR THE DECLARATION

COPY (PCT Rule 44.1)

Date of mailing  
(day/month/year) 18/05/2000

Applicant's or agent's file reference

1719 PCT F

FOR FURTHER ACTION See paragraphs 1 and 4 below

International application No.

PCT/US 99/ 28385

International filing date

(day/month/year) 01/12/1999

Applicant

ALCON LABORATORIES, INC. et al.

1. ☒ The applicant is hereby notified that the International Search Report has been established and is transmitted herewith.

**Filing of amendments and statement under Article 19:**

The applicant is entitled, if he so wishes, to amend the claims of the International Application (see Rule 46):

**When?** The time limit for filing such amendments is normally 2 months from the date of transmittal of the International Search Report; however, for more details, see the notes on the accompanying sheet.

**Where?** Directly to the International Bureau of WIPO  
34, chemin des Colombettes  
1211 Geneva 20, Switzerland  
Facsimile No.: (41-22) 740.14.35

For more detailed instructions, see the notes on the accompanying sheet.

2. ☐ The applicant is hereby notified that no International Search Report will be established and that the declaration under Article 17(2)(a) to that effect is transmitted herewith.

3. ☐ With regard to the protest against payment of (an) additional fee(s) under Rule 40.2, the applicant is notified that:

☐ the protest together with the decision thereon has been transmitted to the International Bureau together with the applicant's request to forward the texts of both the protest and the decision thereon to the designated Offices.

☐ no decision has been made yet on the protest; the applicant will be notified as soon as a decision is made.

4. **Further action(s):** The applicant is reminded of the following:

Shortly after 18 months from the priority date, the international application will be published by the International Bureau. If the applicant wishes to avoid or postpone publication, a notice of withdrawal of the international application, or of the priority claim, must reach the International Bureau as provided in Rules 90bis.1 and 90bis.3, respectively, before the completion of the technical preparations for international publication.

Within 19 months from the priority date, a demand for international preliminary examination must be filed if the applicant wishes to postpone the entry into the national phase until 30 months from the priority date (in some Offices even later).

Within 20 months from the priority date, the applicant must perform the prescribed acts for entry into the national phase before all designated Offices which have not been elected in the demand or in a later election within 19 months from the priority date or could not be elected because they are not bound by Chapter II.

Name and mailing address of the International Searching Authority



European Patent Office, P.B. 5818 Patentlaan 2  
NL-2280 HV Rijswijk  
Tel. (+31-70) 340-2040, Tx. 31 651 po nl,  
Fax: (+31-70) 340-3016

Authorized officer

Claudia Aragone

## NOTES TO FORM PCT/ISA/220

These Notes are intended to give the basic instructions concerning the filing of amendments under article 19. The Notes are based on the requirements of the Patent Cooperation Treaty, the Regulations and the Administrative Instructions under that Treaty. In case of discrepancy between these Notes and those requirements, the latter are applicable. For more detailed information, see also the PCT Applicant's Guide, a publication of WIPO.

In these Notes, "Article", "Rule", and "Section" refer to the provisions of the PCT, the PCT Regulations and the PCT Administrative Instructions respectively.

### INSTRUCTIONS CONCERNING AMENDMENTS UNDER ARTICLE 19

The applicant has, after having received the international search report, one opportunity to amend the claims of the international application. It should however be emphasized that, since all parts of the international application (claims, description and drawings) may be amended during the international preliminary examination procedure, there is usually no need to file amendments of the claims under Article 19 except where, e.g. the applicant wants the latter to be published for the purposes of provisional protection or has another reason for amending the claims before international publication. Furthermore, it should be emphasized that provisional protection is available in some States only.

#### What parts of the international application may be amended?

Under Article 19, only the claims may be amended.

During the international phase, the claims may also be amended (or further amended) under Article 34 before the International Preliminary Examining Authority. The description and drawings may only be amended under Article 34 before the International Examining Authority.

Upon entry into the national phase, all parts of the international application may be amended under Article 28 or, where applicable, Article 41.

#### When?

Within 2 months from the date of transmittal of the international search report or 16 months from the priority date, whichever time limit expires later. It should be noted, however, that the amendments will be considered as having been received on time if they are received by the International Bureau after the expiration of the applicable time limit but before the completion of the technical preparations for international publication (Rule 46.1).

#### Where not to file the amendments?

The amendments may only be filed with the International Bureau and not with the receiving Office or the International Searching Authority (Rule 46.2).

Where a demand for international preliminary examination has been/is filed, see below.

#### How?

Either by cancelling one or more entire claims, by adding one or more new claims or by amending the text of one or more of the claims as filed.

A replacement sheet must be submitted for each sheet of the claims which, on account of an amendment or amendments, differs from the sheet originally filed.

All the claims appearing on a replacement sheet must be numbered in Arabic numerals. Where a claim is cancelled, no renumbering of the other claims is required. In all cases where claims are renumbered, they must be renumbered consecutively (Administrative Instructions, Section 205(b)).

The amendments must be made in the language in which the international application is to be published.

#### What documents must/may accompany the amendments?

##### Letter (Section 205(b)):

The amendments must be submitted with a letter.

The letter will not be published with the international application and the amended claims. It should not be confused with the "Statement under Article 19(1)" (see below, under "Statement under Article 19(1)").

The letter must be in English or French, at the choice of the applicant. However, if the language of the international application is English, the letter must be in English; if the language of the international application is French, the letter must be in French.

## NOTES TO FORM PCT/ISA/220 (continued)

The letter must indicate the differences between the claims as filed and the claims as amended. It must, in particular, indicate, in connection with each claim appearing in the international application (it being understood that identical indications concerning several claims may be grouped), whether

- (i) the claim is unchanged;
- (ii) the claim is cancelled;
- (iii) the claim is new;
- (iv) the claim replaces one or more claims as filed;
- (v) the claim is the result of the division of a claim as filed.

The following examples illustrate the manner in which amendments must be explained in the accompanying letter:

1. [Where originally there were 48 claims and after amendment of some claims there are 51]:  
"Claims 1 to 29, 31, 32, 34, 35, 37 to 48 replaced by amended claims bearing the same numbers; claims 30, 33 and 36 unchanged; new claims 49 to 51 added."
2. [Where originally there were 15 claims and after amendment of all claims there are 11]:  
"Claims 1 to 15 replaced by amended claims 1 to 11."
3. [Where originally there were 14 claims and the amendments consist in cancelling some claims and in adding new claims]:  
"Claims 1 to 6 and 14 unchanged; claims 7 to 13 cancelled; new claims 15, 16 and 17 added." or  
"Claims 7 to 13 cancelled; new claims 15, 16 and 17 added; all other claims unchanged."
4. [Where various kinds of amendments are made]:  
"Claims 1-10 unchanged; claims 11 to 13, 18 and 19 cancelled; claims 14, 15 and 16 replaced by amended claim 14; claim 17 subdivided into amended claims 15, 16 and 17; new claims 20 and 21 added."

### "Statement under article 19(1)" (Rule 46.4)

The amendments may be accompanied by a statement explaining the amendments and indicating any impact that such amendments might have on the description and the drawings (which cannot be amended under Article 19(1)).

The statement will be published with the international application and the amended claims.

**It must be in the language in which the international application is to be published.**

It must be brief, not exceeding 500 words if in English or if translated into English.

It should not be confused with and does not replace the letter indicating the differences between the claims as filed and as amended. It must be filed on a separate sheet and must be identified as such by a heading, preferably by using the words "Statement under Article 19(1)."

It may not contain any disparaging comments on the international search report or the relevance of citations contained in that report. Reference to citations, relevant to a given claim, contained in the international search report may be made only in connection with an amendment of that claim.

### Consequence if a demand for international preliminary examination has already been filed

If, at the time of filing any amendments under Article 19, a demand for international preliminary examination has already been submitted, the applicant must preferably, at the same time of filing the amendments with the International Bureau, also file a copy of such amendments with the International Preliminary Examining Authority (see Rule 62.2(a), first sentence).

### Consequence with regard to translation of the international application for entry into the national phase

The applicant's attention is drawn to the fact that, where upon entry into the national phase, a translation of the claims as amended under Article 19 may have to be furnished to the designated/elected Offices, instead of, or in addition to, the translation of the claims as filed.

For further details on the requirements of each designated/elected Office, see Volume II of the PCT Applicant's Guide.

**PCT**WORLD INTELLECTUAL PROPERTY ORGANIZATION  
International Bureau

## INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

<b>(51) International Patent Classification <sup>7</sup> :</b> <b>A61K 31/522, 31/122, 31/4439, 31/08, 31/7012, A61P 25/02</b>	<b>A1</b>	<b>(11) International Publication Number:</b> <b>WO 00/32197</b> <b>(43) International Publication Date:</b> 8 June 2000 (08.06.00)
<b>(21) International Application Number:</b> PCT/US99/28385 <b>(22) International Filing Date:</b> 1 December 1999 (01.12.99)  <b>(30) Priority Data:</b> 60/110,983 3 December 1998 (03.12.98) US  <b>(71) Applicant (for all designated States except US):</b> ALCON LABORATORIES, INC. [US/US]; 6201 South Freeway, Mail Code Q-149, Fort Worth, TX 76134-2099 (US).  <b>(72) Inventor; and</b> <b>(75) Inventor/Applicant (for US only):</b> PANG, Iok-Hou [US/US]; 125 Starbridge Lane, Grand Prairie, TX 75052 (US).  <b>(74) Agents:</b> MAYO, Michael, C. et al.; Alcon Laboratories, Inc., R & D Counsel, Mail Code Q-148, 6201 South Freeway, Fort Worth, TX 76134-2099 (US).		<b>(81) Designated States:</b> AU, BR, CA, CN, JP, KR, MX, US, ZA, European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE).  <b>Published</b> <i>With international search report. Before the expiration of the time limit for amending the claims and to be republished in the event of the receipt of amendments.</i>
<b>(54) Title:</b> USE OF NEUROTROPHIC FACTOR STIMULATORS FOR THE TREATMENT OF OPHTHALMIC NEURODEGENERATIVE DISEASES  <b>(57) Abstract</b>  Compositions and methods for the treatment of retina and optic nerve head neuropathy are disclosed. The compositions and methods are particularly directed to the use of neurotrophic factor stimulators, such as AIT-082 (neotrofin), in the treatment of glaucomatous neuropathy.		

**FOR THE PURPOSES OF INFORMATION ONLY**

Codes used to identify States party to the PCT on the front pages of pamphlets publishing international applications under the PCT.

AL	Albania	ES	Spain	LS	Lesotho	SI	Slovenia
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DK	Denmark	LK	Sri Lanka	SE	Sweden		
EE	Estonia	LR	Liberia	SG	Singapore		

# INTERNATIONAL SEARCH REPORT

International Application No

PCT/US 99/28385

## A. CLASSIFICATION OF SUBJECT MATTER

IPC 7 A61K31/522 A61K31/122 A61K31/4439 A61K31/08 A61K31/7012  
A61P25/02

According to International Patent Classification (IPC) or to both national classification and IPC

## B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 7 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

## C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 98 10758 A (UNIV CALIFORNIA) 19 March 1998 (1998-03-19) page 3, line 20 - page 4, line 13 page 1, line 22 - line 30 page 5, line 23 - line 37	1,4,5,8, 11,12
X	DATABASE WPI Section Ch, Week 199308 Derwent Publications Ltd., London, GB; Class B05, AN 1993-061598 XP002136481 & JP 05 009114 A (TAKEDA CHEM IND LTD), 19 January 1993 (1993-01-19) abstract	1,2,4,5, 8,9,11, 12

-/-

☒ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

\* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search

10 May 2000

Date of mailing of the international search report

18/05/2000

Name and mailing address of the ISA

European Patent Office, P.B. 5818 Patentlaan 2  
NL - 2280 HV Rijswijk  
Tel. (+31-70) 340-2040, Tx. 31 651 epo nl,  
Fax: (+31-70) 340-3016

Authorized officer

Bonzano, C

## INTERNATIONAL SEARCH REPORT

Inter Application No

PCT/US 99/28385

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT		
Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	HAMMES: "nerve growth factor..." DIABETES RES., vol. 1, no. 5, 1995, pages 527-534, XP000908866 page 530, column 2	8-14
Y	RATHBONE M.P. ET AL: "Physiology and pharmacology of natural and synthetic nonadenine-based purines in the nervous system." DRUG DEVELOPMENT RESEARCH, (1998) 45/3-4 (356-372). , XP000904784	8-14
X	page 363, column 2, paragraph 3 -page 365, column 1, paragraph 1	1-7
Y	MIDDLEMISS P J ET AL: "AIT - 082, a unique purine derivative, enhances nerve growth factor mediated neurite outgrowth from PC1 cells." NEUROSCIENCE LETTERS, (1995 OCT 20) 199 (2) 131-4. , XP000905256	8-14
X	page 402, column 1, paragraph 6 -column 2, paragraph 3 page 403, column 1, paragraph 3	1-7
Y	YAMAMOTO K ET AL: "Neuroprotective effect of 4'-(4-methylphenyl)-2,2':6',2-terpyridine trihydrochloride, a novel inducer of nerve growth factor." LIFE SCIENCES, (1996) 59 (25-26) 2139-46. , XP000904780	8,9,11, 12
X	page 2144, paragraph 1	1,2,4,5
Y	NITTA A ET AL: "Oral administration of idebenone induces nerve— growth factor in the brain and improves learning and memory in basal forebrain-lesioned rats." NAUNYN-SCHMIEDEBERGS ARCHIVES OF PHARMACOLOGY, (1994 APR) 349 (4) 401-7. , XP000904765	8,9,11, 12
X	page 401, column 2, paragraph 3 -page 402, column 1, paragraph 2 abstract	1,2,4,5
Y	CULMSEE, C. ET AL: "Neuroprotection by drug-induced growth factors" PHARMACOL. CEREB. ISCHEMIA 1998, 'INT. SYMP.!', 7TH (1999), 333-348. EDITOR(S): KRIEGLSTEIN, JOSEF. PUBLISHER: MEDPHARM SCIENTIFIC PUBLISHERS, STUTTGART, GERMANY. , XP000905223	8,9,11, 12
X	page 334, column 2, paragraph 1	1,2,4,5
	—/—	



## INTERNATIONAL SEARCH REPORT

Inter Application No

PCT/US 99/28385

## C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	SEMKOVA I ET AL: "Clenbuterol protects mouse cerebral cortex and rat hippocampus from ischemic damage and attenuates glutamate neurotoxicity in cultured hippocampal neurons by induction of NGF." BRAIN RESEARCH, (1996 APR 22) 717 (1-2) 44-54. , XP000904807	8,9,11, 12
X	page 49, column 2, paragraph 2	1,2,4,5
P,Y	RIAZ S ET AL: "A vitamin D(3) derivative (CB1093) induces nerve growth factor and prevents neurotrophic deficits in streptozotocin-diabetic rats." DIABETOLOGIA, (1999 NOV) 42 (11) 1308-13. , XP000901997	8,9,11, 12
P,X	page 1311, column 2, paragraph 2 -page 1312, column 1, paragraph 1	1,2,4,5
P,Y	GRONBORG M ET AL: "Neuroprotection by a novel compound, NS521." JOURNAL OF PHARMACOLOGY AND EXPERIMENTAL THERAPEUTICS, (1999 JUL) 290 (1) 348-53. , XP000904771	8,9,11, 12
P,X	page 348, column 1 -column 2	1,2,4,5
A	US 5 641 750 A (LOUIS JEAN-CLAUDE) 24 June 1997 (1997-06-24) column 3, paragraph 4 column 4, paragraph 4 -column 5, paragraph 1	8-14

# INTERNATIONAL SEARCH REPORT

International application No.

PCT/US 99/28385

## Box I Observations where certain claims were found unsearchable (Continuation of Item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claims Nos.: 8-14  
because they relate to subject matter not required to be searched by this Authority, namely:  
Remark: Although claims 8-14  
are directed to a method of treatment of the human/animal  
body, the search has been carried out and based on the alleged  
effects of the compound/composition.
2. ☒ Claims Nos.: -  
because they relate to parts of the International Application that do not comply with the prescribed requirements to such  
an extent that no meaningful International Search can be carried out, specifically:  
See FURTHER INFORMATION SHEET PCT/ISA/210
3. ☐ Claims Nos.:  
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

## Box II Observations where unity of invention is lacking (Continuation of Item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this International Search Report covers all  
searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment  
of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this International Search Report  
covers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is  
restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest.
- ☐ No protest accompanied the payment of additional search fees.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

## Continuation of Box I.2

Present claims 1,4,5,8,11,12 relate to compounds defined by reference to a desirable pharmacological property, namely the activity as neurotrophic factor stimulators.

The claims cover all compounds having this characteristic or property, whereas the application provides support within the meaning of Article 6 PCT and/or disclosure within the meaning of Article 5 PCT for only a very limited number of such compounds. In the present case, the claims so lack support, and the application so lacks disclosure, that a meaningful search over the whole of the claimed scope is not fully possible. Independent of the above reasoning, the claims also lack clarity (Article 6 PCT). An attempt is made to define the compounds by reference to their pharmacological profiles. Again, this lack of clarity in the present case is such as to render a meaningful search over the whole of the claimed scope impossible. Consequently, the search has been carried out for those parts of the claims which appear to be clear, supported and disclosed, namely those parts relating to the compounds structurally identified in claim 2 with due regard to the general idea underlying the present invention.

Claims searched completely: 2,3,6,7,9,10,13,14.

Claims searched incompletely: 1,4,5,8,11,12.

The applicant's attention is drawn to the fact that claims, or parts of claims, relating to inventions in respect of which no international search report has been established need not be the subject of an international preliminary examination (Rule 66.1(e) PCT). The applicant is advised that the EPO policy when acting as an International Preliminary Examining Authority is normally not to carry out a preliminary examination on matter which has not been searched. This is the case irrespective of whether or not the claims are amended following receipt of the search report or during any Chapter II procedure.

# INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/US 99/28385

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 9810758 A	19-03-1998	AU 4582797 A	02-04-1998
JP 5009114 A	19-01-1993	NONE	
US 5641750 A	24-06-1997	AU 698062 B	22-10-1998
		AU 1059297 A	19-06-1997
		BR 9611750 A	06-04-1999
		CN 1203532 A	30-12-1998
		CZ 9801544 A	12-05-1999
		EP 0863766 A	16-09-1998
		HU 9802374 A	01-02-1999
		JP 2000502057 T	22-02-2000
		NO 982275 A	29-07-1998
		SK 65998 A	10-09-1999
		WO 9719694 A	05-06-1997
		US 5736516 A	07-04-1998

# PATENT COOPERATION TREATY

From the  
INTERNATIONAL PRELIMINARY EXAMINING AUTHORITY

COPY PCT

To: MICHAEL C. MAYO  
ALCON LABORATORIES, INC.  
6201 SOUTH FREEWAY  
MAIL CODE Q-148  
FORT WORTH TX 76134-2099

## NOTIFICATION OF TRANSMITTAL OF INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Rule 71.1)

Date of Mailing  
(day/month/year)

20 MAY 2001

Applicant's or agent's file reference  
1719 PCT F

### IMPORTANT NOTIFICATION

International application No.  
PCT/US99/28385

International filing date (day/month/year)  
01 DECEMBER 1999

Priority Date (day/month/year)  
03 DECEMBER 1998

Applicant  
ALCON LABORATORIES, INC.

RECEIVED

MAR 27 2001

SSY

1. The applicant is hereby notified that this International Preliminary Examining Authority transmits herewith the international preliminary examination report and its annexes, if any, established on the international
2. A copy of the report and its annexes, if any, is being transmitted to the International Bureau for communication to all the elected Offices.
3. Where required by any of the elected Offices, the International Bureau will prepare an English translation of the report (but not of any annexes) and will transmit such translation to those Offices.
4. REMINDER

The applicant must enter the national phase before each elected Office by performing certain acts (filing translations and paying national fees) within 30 months from the priority date (or later in some Offices) (Article 39(1)) (see also the reminder sent by the International Bureau with Form PCT/IB/301).

Where a translation of the international application must be furnished to an elected Office, that translation must contain a translation of any annexes to the international preliminary examination report. It is the applicant's responsibility to prepare and furnish such translation directly to each elected Office concerned.

For further details on the applicable time limits and requirements of the elected Offices, see Volume II of the PCT Applicant's Guide.

Name and mailing address of the IPEA/US  
Commissioner of Patents and Trademarks  
Box PCT  
Washington, D.C. 20231

Facsimile No. (703) 305-3230

Authorized officer

ZONREH FAY

Telephone No. (703) 308-1235

# PATENT COOPERATION TREATY

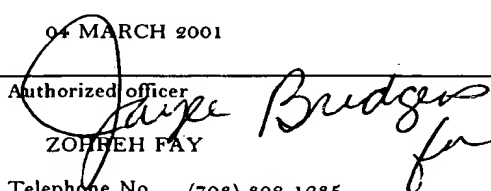
## PCT

### INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference 1719 PCT F	<b>FOR FURTHER ACTION</b> See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)	
International application No. PCT/US99/28385	International filing date (day/month/year) 01 DECEMBER 1999	Priority date (day/month/year) 03 DECEMBER 1998
International Patent Classification (IPC) or national classification and IPC IPC(7):A61K 31/445 and US Cl.: 514/316, 912		
Applicant ALCON LABORATORIES, INC.		

1.	This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.
2.	This REPORT consists of a total of <u>3</u> sheets.  <input type="checkbox"/> This report is also accompanied by ANNEXES, i.e., sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority. (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).  These annexes consist of a total of <u>0</u> sheets.
3.	This report contains indications relating to the following items: <ul style="list-style-type: none"> <li>I <input checked="" type="checkbox"/> Basis of the report</li> <li>II <input type="checkbox"/> Priority</li> <li>III <input type="checkbox"/> Non-establishment of report with regard to novelty, inventive step or industrial applicability</li> <li>IV <input type="checkbox"/> Lack of unity of invention</li> <li>V <input checked="" type="checkbox"/> Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability, citations and explanations supporting such statement</li> <li>VI <input type="checkbox"/> Certain documents cited</li> <li>VII <input type="checkbox"/> Certain defects in the international application</li> <li>VIII <input type="checkbox"/> Certain observations on the international application</li> </ul>

Date of submission of the demand  05 JUNE 2000	Date of completion of this report  04 MARCH 2001
Name and mailing address of the IPEA/US Commissioner of Patents and Trademarks Box PCT Washington, D.C. 20231	Authorized officer  ZOZREH FAY
Facsimile No. (703) 305-3230	Telephone No. (703) 308-1235

## INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No.

PCT/US99/28385

**I. Basis of the report****1. With regard to the elements of the international application:\***

- ☒ the international application as originally filed
- ☒ the description:  
pages 1-17, as originally filed  
pages NONE, filed with the demand  
pages NONE, filed with the letter of \_\_\_\_\_
- ☒ the claims:  
pages 18-19, as originally filed  
pages NONE, as amended (together with any statement) under Article 19  
pages NONE, filed with the demand  
pages NONE, filed with the letter of \_\_\_\_\_
- ☒ the drawings:  
pages NONE, as originally filed  
pages NONE, filed with the demand  
pages NONE, filed with the letter of \_\_\_\_\_
- ☒ the sequence listing part of the description:  
pages NONE, as originally filed  
pages NONE, filed with the demand  
pages NONE, filed with the letter of \_\_\_\_\_

**2. With regard to the language, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.**

These elements were available or furnished to this Authority in the following language \_\_\_\_\_ which is:

- ☐ the language of a translation furnished for the purposes of international search (under Rule 23.1(b)).
- ☐ the language of publication of the international application (under Rule 48.3(b)).
- ☐ the language of the translation furnished for the purposes of international preliminary examination (under Rules 55.2 and/or 55.3).

**3. With regard to any nucleotide and/or amino acid sequence disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:**

- ☐ contained in the international application in printed form.
- ☐ filed together with the international application in computer readable form.
- ☐ furnished subsequently to this Authority in written form.
- ☐ furnished subsequently to this Authority in computer readable form.
- ☐ The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.
- ☐ The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

**4. ☒ The amendments have resulted in the cancellation of:**

- ☒ the description, pages NONE
- ☒ the claims, Nos. NONE
- ☒ the drawings, sheets/fig. NONE

**5. ☐ This report has been drawn as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed, as indicated in the Supplemental Box (Rule 70.2(c)).\*\***

\* Replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report since they do not contain amendments (Rules 70.16 and 70.17).

\*\*Any replacement sheet containing such amendments must be referred to under item 1 and annexed to this report.

# INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No.

PCT/US99/28385

## V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

### 1. statement

Novelty (N)	Claims	<u>1-14</u>	YES
	Claims	<u>NONE</u>	NO
Inventive Step (IS)	Claims	<u>NONE</u>	YES
	Claims	<u>1-14</u>	NO
Industrial Applicability (IA)	Claims	<u>NONE</u>	YES
	Claims	<u>1-14</u>	NO

### 2. citations and explanations (Rule 70.7)

Claims 1-14 lack an inventive step under PCT Article 33(3) as being obvious over UNIV CALIFORNIA (WO 98/10758). The UNIV CALIFORNIA teaches the use of an alpha adrenergic agonists or betaadrenergic agonists for the treatment of retinal disorders. In view of the above reference the claimed composition or the use thereof does not involve an inventive step.

\_\_\_\_ NEW CITATIONS \_\_\_\_\_  
NONE



# PATENT COOPERATION TREATY

From the  
INTERNATIONAL PRELIMINARY EXAMINING AUTHORITY

To: MICHAEL C. MAYO  
ALCON LABORATORIES, INC.  
6201 SOUTH FREEWAY  
MAIL CODE Q-148  
FORT WORTH TX 76134-2099

COPY

PCT

WRITTEN OPINION

(PCT Rule 66)

Date of Mailing  
(day/month/year)

24 OCT 2000

Applicant's or agent's file reference  
1719 PCT F

**REPLY DUE** within TWO months  
from the above date of mailing

International application No.  
PCT/US99/28385

International filing date (day/month/year)  
01 DECEMBER 1999

Priority date (day/month/year)  
03 DECEMBER 1998

International Patent Classification (IPC) or both national classification and IPC  
IPC(7):A61K 31/445 and US Cl.: 514/316, 912

Applicant  
ALCON LABORATORIES, INC.

1. This written opinion is the first (first, etc.) drawn by this International Preliminary Examining Authority.

2. This opinion contains indications relating to the following items:

- I ☒ Basis of the opinion
- II ☐ Priority
- III ☐ Non-establishment of opinion with regard to novelty, inventive step or industrial applicability
- IV ☐ Lack of unity of invention
- V ☒ Reasoned statement under Rule 66.2(a)(ii) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
- VI ☐ Certain documents cited
- VII ☐ Certain defects in the international application
- VIII ☐ Certain observations on the international application

RECEIVED

OCT 27 2000

SSY

3. The applicant is hereby invited to reply to this opinion.

**When?** See the time limit indicated above. ~~The applicant may, before the expiration of that time limit, request this Authority to grant an extension, see Rule 66.2(d).~~

**How?** By submitting a written reply, accompanied, where appropriate, by amendments, according to Rule 66.3. For the form and the language of the amendments, see Rules 66.8 and 66.9.

**Also** For an additional opportunity to submit amendments, see Rule 66.4.  
For the examiner's obligation to consider amendments and/or arguments, see Rule 66.4 bis.  
For an informal communication with the examiner, see Rule 66.6.

If no reply is filed, the international preliminary examination report will be established on the basis of this opinion.

4. The final date by which the international preliminary examination report must be established according to Rule 69.2 is: 03 APRIL 2001

Name and mailing address of the IPEA/US  
Commissioner of Patents and Trademarks  
Box PCT  
Washington, D.C. 20231

Facsimile No. (703) 305-3230

Authorized officer

ZOHREH FAY

Telephone No. (703) 308-1235

WRITTEN OPINION

International application No.

PCT/US99/28385

**I. Basis of the opinion**

1. With regard to the **elements** of the international application:\*

- ☒ the international application as originally filed
- ☒ the description:  
 pages 1-17 , as originally filed  
 pages NONE , filed with the demand  
 pages NONE , filed with the letter of \_\_\_\_\_
- ☒ the claims:  
 pages 18-19 , as originally filed  
 pages NONE , as amended (together with any statement) under Article 19  
 pages NONE , filed with the demand  
 pages NONE , filed with the letter of \_\_\_\_\_
- ☒ the drawings:  
 pages NONE , as originally filed  
 pages NONE , filed with the demand  
 pages NONE , filed with the letter of \_\_\_\_\_
- ☒ the sequence listing part of the description:  
 pages NONE , as originally filed  
 pages NONE , filed with the demand  
 pages NONE , filed with the letter of \_\_\_\_\_

2. With regard to the **language**, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.  
 These elements were available or furnished to this Authority in the following language \_\_\_\_\_ which is:

- ☐ the language of a translation furnished for the purposes of international search (under Rule 23.1(b)).
- ☐ the language of publication of the international application (under Rule 48.3(b)).
- ☐ the language of the translation furnished for the purposes of international preliminary examination (under Rules 55.2 and/or 55.3).

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the written opinion was drawn on the basis of the sequence listing:

- ☐ contained in the international application in printed form.
- ☐ filed together with the international application in computer readable form.
- ☐ furnished subsequently to this Authority in written form.
- ☐ furnished subsequently to this Authority in computer readable form.
- ☐ The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.
- ☐ The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

4. ☒ The amendments have resulted in the cancellation of:

- ☒ the description, pages NONE
- ☒ the claims, Nos. NONE
- ☒ the drawings, sheets/fig NONE

5. ☐ This opinion has been drawn as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed, as indicated in the Supplemental Box (Rule 70.2(c)).

\* Replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this opinion as "originally filed".

## WRITTEN OPINION

International application No.

PCT/US99/28385

**V. Reasoned statement under Rule 66.2(a)(ii) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement**

## 1. statement

Novelty (N)	Claims	<u>1-14</u>	YES
	Claims	<u>NONE</u>	NO
Inventive Step (IS)	Claims	<u>NONE</u>	YES
	Claims	<u>1-14</u>	NO
Industrial Applicability (IA)	Claims	<u>NONE</u>	YES
	Claims	<u>1-14</u>	NO

## 2. citations and explanations

Claims 1-14 lack an inventive step under PCT Article 33(3) as being obvious over UNIV CALIFORNIA (WO 98/10758). The UNIV CALIFORNIA teaches the use of an alpha adrenergic agonists or betaadrenergic agonists for the treatment of retinal disorders. In view of the above reference the claimed composition or the use thereof does not involve an inventive step.

----- NEW CITATIONS -----  
NONE

WRITTEN OPINION

International application No.

PCT/US99/28385

**Supplemental Box**

(To be used when the space in any of the preceding boxes is not sufficient)

Continuation of: Boxes I - VIII

Sheet 10

**TIME LIMIT:**

The time limit set for response to a Written Opinion may not be extended. 37 CFR 1.484(d). Any response received after the expiration of the time limit set in the Written Opinion will not be considered in preparing the International Preliminary Examination Report.

# PCT

## INTERNATIONAL SEARCH REPORT

(PCT Article 18 and Rules 43 and 44)

Applicant's or agent's file reference <b>1719 PCT F</b>	<b>FOR FURTHER ACTION</b> see Notification of Transmittal of International Search Report (Form PCT/ISA/220) as well as, where applicable, item 5 below.	
International application No. <b>PCT/US 99/ 28385</b>	International filing date (day/month/year) <b>01/12/1999</b>	(Earliest) Priority Date (day/month/year) <b>03/12/1998</b>
Applicant <b>ALCON LABORATORIES, INC. et al.</b>		

This International Search Report has been prepared by this International Searching Authority and is transmitted to the applicant according to Article 18. A copy is being transmitted to the International Bureau.

This International Search Report consists of a total of 6 sheets.



It is also accompanied by a copy of each prior art document cited in this report.

**1. Basis of the report**

- a. With regard to the language, the International search was carried out on the basis of the International application in the language in which it was filed, unless otherwise indicated under this item.



the International search was carried out on the basis of a translation of the International application furnished to this Authority (Rule 23.1(b)).

- b. With regard to any nucleotide and/or amino acid sequence disclosed in the International application, the International search was carried out on the basis of the sequence listing :



contained in the International application in written form.



filed together with the International application in computer readable form.



furnished subsequently to this Authority in written form.



furnished subsequently to this Authority in computer readable form.



the statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the International application as filed has been furnished.



the statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished

2. ☒ **Certain claims were found unsearchable** (See Box I).

3. ☐ **Unity of invention is lacking** (see Box II).

**4. With regard to the title,**



the text is approved as submitted by the applicant.



the text has been established by this Authority to read as follows:

**5. With regard to the abstract,**



the text is approved as submitted by the applicant.



the text has been established, according to Rule 38.2(b), by this Authority as it appears in Box III. The applicant may, within one month from the date of mailing of this International search report, submit comments to this Authority.

**6. The figure of the drawings to be published with the abstract is Figure No.**



as suggested by the applicant.



because the applicant failed to suggest a figure.



because this figure better characterizes the invention.



None of the figures.

# INTERNATIONAL SEARCH REPORT

International application No.

PCT/US 99/ 28385

## Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claims Nos.: 8-14  
because they relate to subject matter not required to be searched by this Authority, namely:  
Remark: Although claims 8-14  
are directed to a method of treatment of the human/animal  
body, the search has been carried out and based on the alleged  
effects of the compound/composition.
2. ☒ Claims Nos.: -  
because they relate to parts of the International Application that do not comply with the prescribed requirements to such  
an extent that no meaningful International Search can be carried out, specifically:  
See FURTHER INFORMATION SHEET PCT/ISA/210
3. ☐ Claims Nos.:  
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

## Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this International application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this International Search Report covers all  
searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment  
of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this International Search Report  
covers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is  
restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest.
- ☐ No protest accompanied the payment of additional search fees.

# PATENT COOPERATION TREATY

## PCT

### INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

REC'D 23 MAR 2001

WIPO PCT

Applicant's or agent's file reference 1719 PCT F	<b>FOR FURTHER ACTION</b> See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)	
International application No. PCT/US99/28385	International filing date (day/month/year) 01 DECEMBER 1999	Priority date (day/month/year) 03 DECEMBER 1998
International Patent Classification (IPC) or national classification and IPC IPC(7):A61K 31/445 and US Cl.: 514/516, 912		
Applicant ALCON LABORATORIES, INC.		

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.
2. This REPORT consists of a total of 3 sheets.
 

☐ This report is also accompanied by ANNEXES, i.e., sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority. (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

These annexes consist of a total of 0 sheets.

3. This report contains indications relating to the following items:

- I ☒ Basis of the report
- II ☐ Priority
- III ☐ Non-establishment of report with regard to novelty, inventive step or industrial applicability
- IV ☐ Lack of unity of invention
- V ☒ Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability, citations and explanations supporting such statement
- VI ☐ Certain documents cited
- VII ☐ Certain defects in the international application
- VIII ☐ Certain observations on the international application

Date of submission of the demand  05 JUNE 2000	Date of completion of this report  04 MARCH 2001
Name and mailing address of the IPEA/US Commissioner of Patents and Trademarks Box PCT Washington, D.C. 20231	Authorized officer  ZOHREH FAY
Facsimile No. (703) 305-3230	Telephone No. (703) 308-1235

## INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No.

PCT/US99/28385

## I. Basis of the report

## 1. With regard to the elements of the international application:\*

☒ the international application as originally filed☒ the description:

pages 1-17, as originally filed  
pages NONE, filed with the demand  
pages NONE, filed with the letter of

☒ the claims:

pages 18-19, as originally filed  
pages NONE, as amended (together with any statement) under Article 19  
pages NONE, filed with the demand  
pages NONE, filed with the letter of

☒ the drawings:

pages NONE, as originally filed  
pages NONE, filed with the demand  
pages NONE, filed with the letter of

☒ the sequence listing part of the description:

pages NONE, as originally filed  
pages NONE, filed with the demand  
pages NONE, filed with the letter of

## 2. With regard to the language, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.

These elements were available or furnished to this Authority in the following language which is:

- ☐ the language of a translation furnished for the purposes of international search (under Rule 23.1(b)).  
☐ the language of publication of the international application (under Rule 48.3(b)).  
☐ the language of the translation furnished for the purposes of international preliminary examination (under Rules 55.2 and/or 55.3).

## 3. With regard to any nucleotide and/or amino acid sequence disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:

- ☐ contained in the international application in printed form.  
☐ filed together with the international application in computer readable form.  
☐ furnished subsequently to this Authority in written form.  
☐ furnished subsequently to this Authority in computer readable form.  
☐ The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.  
☐ The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

4. ☒ The amendments have resulted in the cancellation of:

☒ the description, pages NONE  
☒ the claims, Nos. NONE  
☒ the drawings, sheets/fig. NONE

5. ☐ This report has been drawn as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed, as indicated in the Supplemental Box (Rule 70.2(c)).\*\*

\* Replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report since they do not contain amendments (Rules 70.16 and 70.17).

\*\*Any replacement sheet containing such amendments must be referred to under item 1 and annexed to this report.



# INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No.

PCT/US99/28385

## V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

### 1. statement

Novelty (N)	Claims	<u>1-14</u>	YES
	Claims	<u>NONE</u>	NO
Inventive Step (IS)	Claims	<u>NONE</u>	YES
	Claims	<u>1-14</u>	NO
Industrial Applicability (IA)	Claims	<u>NONE</u>	YES
	Claims	<u>1-14</u>	NO

### 2. citations and explanations (Rule 70.7)

Claims 1-14 lack an inventive step under PCT Article 33(3) as being obvious over UNIV CALIFORNIA (WO 98/10758). The UNIV CALIFORNIA teaches the use of an alpha adrenergic agonists or betaadrenergic agonists for the treatment of retinal disorders. In view of the above reference the claimed composition or the use thereof does not involve an inventive step.

NEW CITATIONS

NONE